FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 1768

U.S APPLICATION NO. (If known, see 37 CFR 1 5): 09/868441

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/01719	16 June 1999	16 December 1998

TITLE OF INVENTION: PROCESS FOR PREPARING POLYAMINES

APPLICANT(S) FOR DO/EO/US: James L. Payne and Neal D. Hone

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [X] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

JC03 Rec'd PCT/PTC 18 JUN 2001

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/868441	PCT/GB99/01719	1768

21. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	27 - 20 =	7	x **$18.00**	$ 126.00	
Independent claims	8 - 3 =	5	x **$80.00**	$ 400.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,386.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 1,386.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1,386.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $ 1,386.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-1940. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Timothy J. Martin, P.C.
9250 W. 5th Avenue, Suite 200
Lakewood, Colorado 80226
(303) 232-3388

SIGNATURE

Mark H. Weygandt
NAME

43,260
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Patent Application for	:	Date: June 18, 2001
	Payne et al.	:	Art Unit:
Ser. No.:		:	Examiner:
Filed:	June 18, 2001	:	Action: ***PRELIMINARY***
	National Stage	:	***AMENDMENT***
	Application of PCT/GB99/01719	:	
For:	***PROCESS FOR PREPARING***	:	
	POLYAMINES	:	

To: The Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Please amend the above-identified patent application as follows:

In the claims:

Kindly replace the claims pages on file with the attached Clean Copy Of Pending Claims Including Amendments Made June 18, 2001, Pursuant To 37 C.F.R. §1.121(c)(3). A Marked-Up Version of Amended Claims Pursuant To 37 C.F.R. §1.121(c)(1)(ii) is also attached hereto, showing the changes made by Microsoft Word 2000 redline method. This Amendment amends claims 1, 3 - 6 and 9 - 15, cancels claims 16 - 19, and adds claims 20 - 27.

Remarks

The present Preliminary Amendment is submitted in regard to the U.S. National Stage Application of PCT/GB99/01719. Filed concurrently herewith is a Form PTO-1390 (Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 U.S.C. 371) in regard to the above-identified application. The claim fees as set forth therein are calculated pursuant to the amendments to the claims made in the present Preliminary Amendment. However, the Commissioner is

hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 13-1940.

Applicants respectfully request that the Examiner enter an allowance of all claims in this case. Action to that end is courteously solicited. If any issues remain to be resolved, it is respectfully requested that the Examiner contact the undersigned attorney for the Applicant at the number listed below.

Respectfully submitted,

TIMOTHY J. MARTIN, P.C.

Timothy J. Martin, #28,640
Michael R. Henson, #39,222
Mark H. Weygandt, #43,260
9250 W. 5th Avenue, Suite 200
Lakewood, Colorado 80226
(303) 232-3388

Clean Copy of Pending Claims Including Amendments Made June 18, 2001, Pursuant to 37 C.F.R. §1.121(c)(3)

1. (Once Amended) A process for preparing a polyamine compound, comprising treating a compound which incorporates a moiety of formula:

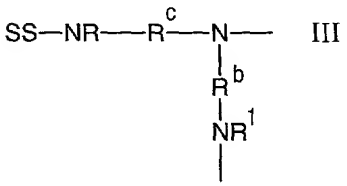
$$SS\text{-}NR\text{-}R^{c}\text{-}NH\text{-} \qquad I$$

with a compound which incorporates a moiety of formula:

$$\text{-}NR^{1}\text{-}R^{b}\text{-}L \qquad II$$

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

2. A process according to claim 1, wherein said process produces a compound which incorporates a moiety:



III

3. (Once Amended) A process according to claim 1, wherein said moiety of formula I is part of a structure of formula:

$$SS\text{-}NR\text{-}R^{c}\text{-}NHP^{1} \qquad IV$$

wherein P^1 represents a group selected from a protecting group and an activating group.

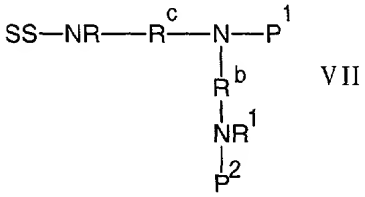
Clean Copy of Pending Claims Including Amendments Made June 18, 2001, Pursuant to 37 C.F.R. §1.121(c)(3)

4. (Once Amended) A process according to claim 1, wherein said moiety of formula II is part of a structure of formula:

$P^2NR^1\text{-}R^b\text{-}L$

wherein P^2 represents a protecting group.

5. (Once Amended) A process according to claim 1, wherein the product of the reaction of moieties of formula I and II is of formula



VII

wherein P^1 represents a group selected from a protecting group and an activating group and P^2 represents a protecting group.

6. (Once Amended) A process according to claim 1, wherein the polyamine prepared by reacting moieties I and II is derivatised in a subsequent process step.

7. A process according to claim 6, wherein derivatisation involves treatment with a first reagent in order to incorporate a residue of said first reagent into said polyamine.

8. A process according to claim 7, wherein said first reagent is difunctional.

9. (Once Amended) A process according to claim 7, wherein said first reagent includes an amine group or a precursor of an amine group.

Clean Copy of Pending Claims Including Amendments Made June 18, 2001, Pursuant to 37 C.F.R. §1.121(c)(3)

10. (Once Amended) A process according to claim 7, wherein said first reagent is an amino acid or a precursor thereof.

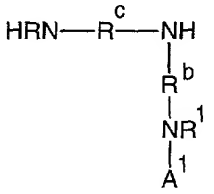
11. (Once Amended) A process according to claim 7, wherein said polyamine is derivatised with a second reagent.

12. (Once Amended) A process according to claim 1, wherein R represents a hydrogen atom or an optionally-substituted alkyl group; R^b and R^c independently have up to 10 carbon atoms in a straight chain; R^1 represents a hydrogen atom or an optionally-substituted C_{1-10} alkyl group or an optionally-substituted aryl group.

13. (Once Amended) A process according to claim 1, wherein L is an electron-withdrawing group.

14. (Once Amended) A process according to claim 1, wherein L represents a halogen atom or an hydroxy group.

15. (Once Amended) A process according to claim 1, wherein the compound prepared in the process is of general formula



wherein A^1 is a substituent group.

16. (Canceled)

17. (Canceled)

18. (Canceled)

Clean Copy of Pending Claims Including Amendments Made June 18, 2001, Pursuant to 37 C.F.R. §1.121(c)(3)

19. (Canceled)

20. (New) A process for preparing a plurality of different polyamine compounds, comprising:

(a) selecting a plurality of different compounds which include moiety I of the formula:

SS-NR-R^c-NH- I

(b) selecting a plurality of different compounds which include moiety II of the formula:

-NR^1-R^b-L II

and

(c) reacting compounds which include moiety I with compounds which include moiety II, followed by optional derivatisation, thereby to prepare a plurality of different polyamine compounds, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

21. (New) A process for preparing a plurality of different polyamine compounds, comprising derivatising a product of a reaction of a compound including moiety I of the formula:

SS-NR-R^c-NH- I

with a compound including moiety II of the formula:

$-NR^1-R^b-L$ II

with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

22. (New) A chemical compound prepared by a process comprising treating a compound which incorporates a moiety of formula:

$SS-NR-R^c-NH-$ I

with a compound which incorporates a moiety of formula:

$-NR^1-R^b-L$ II

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

23. (New) A library of compounds prepared by a process comprising:

(a) selecting a plurality of different compounds which include moiety I of the formula:

SS-NR-R^c-NH- I

(b) selecting a plurality of different compounds which include moiety II of the formula:

-NR^1-R^b-L II

and

(c) reacting compounds which include moiety I with compounds which include moiety II, followed by optional derivatisation, thereby to prepare a plurality of different polyamine compounds, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

24. (New) A library of compounds prepared by a process comprisingderivatising a product of a reaction of a compound including moiety I of the formula:

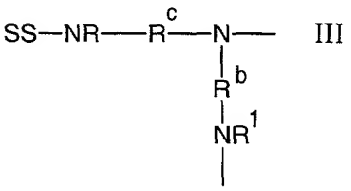
SS-NR-R^c-NH- I

with a compound including moiety II of the formula:

-NR^1-R^b-L II

with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

25. (New) A chemical compound which incorporates a moiety:

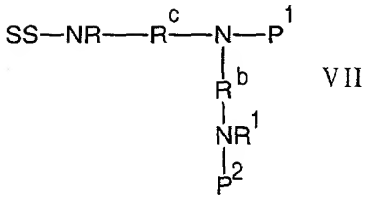


III

wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, and R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group.

26. (New) A chemical compound according to claim 25, wherein said chemical compound is of formula

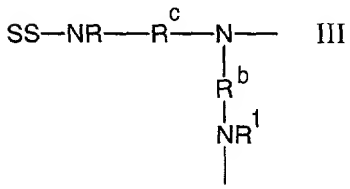
Clean Copy of Pending Claims Including Amendments Made June 18, 2001, Pursuant to 37 C.F.R. §1.121(c)(3)



VII

wherein P^1 represents a group selected from a protecting group and an activating group and P^2 represents a protecting group.

27. (New) A chemical compound comprising a derivative of a compound which incorporates a moiety:



III

wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, and R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group.

Marked-Up Version of Amended Claims Pursuant To 37 C.F.R. §1.121(c)(1)(ii)

1. (Once Amended) A process for preparing a polyamine compound, comprising ~~which includes a step (a) of~~ treating a compound which incorporates a moiety of formula:

SS-NR-R^c-NH- I

with a compound which incorporates a moiety of formula:

-NR^1-R^b-L II

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group –NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

3. (Once Amended) A process according to claim 1 ~~or claim 2~~, wherein said moiety of formula I is part of a structure of formula:

SS-NR-R^c-NHP^1 IV

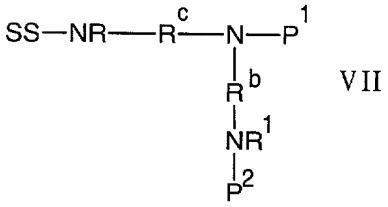
wherein P^1 represents a group selected from a protecting group and/~~or~~ an activating group.

4. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein said moiety of formula II is part of a structure of formula:

P^2NR^1-R^b-L

wherein P^2 represents a protecting group.

5. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein the product of the reaction of moieties of formula I and II is of formula



VII

wherein P^1 represents a group selected from a protecting group and~~/or~~ an activating group and P^2 represents a protecting group.

6. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein the polyamine prepared by reacting moieties I and II ~~and/or moiety III and/or moiety VII are~~ is derivatised in a subsequent process step.

9. (Once Amended) A process according to claim 7 ~~or claim 8~~, wherein said first reagent includes an amine group or a precursor of an amine group.

10. (Once Amended) A process according to ~~any of~~ claim~~s~~ 7 ~~to 9~~, wherein said first reagent is an amino acid or a precursor thereof.

11. (Once Amended) A process according to ~~any of~~ claim~~s~~ 7 ~~to 10~~, wherein said polyamine is derivatised with a second reagent.

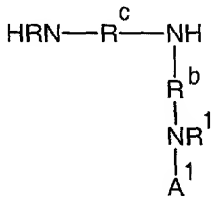
12. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein R represents a hydrogen atom or an optionally-substituted alkyl group; R^b and R^c independently have up to 10 carbon atoms in a straight chain; R^1 represents a hydrogen atom or an optionally-substituted C_{1-10} alkyl group or an optionally-substituted aryl group.

13. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein L is an electron-withdrawing group.

Marked-Up Version of Amended Claims Pursuant To 37 C.F.R. §1.121(c)(1)(ii)

14. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein L represents a halogen atom or an hydroxy group.

15. (Once Amended) A process according to ~~any preceding~~ claim 1, wherein the compound prepared in the process is of general formula



wherein A^1 is a substituent group.

#3
PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: Patent Application for Payne et al.
Ser. No.: 09/868,441
Filed: June 18, 2001
National Stage Application of: PCT/GB99/01719
For: ***PROCESS FOR PREPARING POLYAMINES***

Date: August 20, 2001
Art Unit:
Examiner:
Action: ***PRELIMINARY AMENDMENT***

To: The Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Please amend the above-identified patent application as follows:

In the specification:

Pursuant to 37 C.F.R. §§ 1.78 and 1.121(b), please add the following paragraph immediately after the Title of the application on page 1:

> The present application is a 35 U.S.C. 371 national stage application of international application PCT/GB99/01719 designating the United States of America, which was filed on June 16, 1999 and published in English on June 22, 2000 as WO 00/35941, which claims priority through copending international application PCT/GB98/03775 designating the United States of America, which was filed on December 16, 1998 and published in English on June 24, 1999 as WO 99/31049.

Remarks

This Preliminary Amendment is submitted in regard to the present U.S. National Stage Application of PCT/GB99/01719. The above amendment inserts a reference in the first sentence following the title, pursuant to 37 C.F.R. §1.78, to the

copending international application PCT/GB98/03775 designating the United States of America, from which the present application claims priority.

While no fees are believed payable upon this amendment, the Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 13-1940.

Applicants respectfully request that the Examiner enter an allowance of all claims in this case. Action to that end is courteously solicited. If any issues remain to be resolved, it is respectfully requested that the Examiner contact the undersigned attorney for the Applicant at the number listed below.

Respectfully submitted,

TIMOTHY J. MARTIN, P.C.

Timothy J. Martin, #28,640
Michael R. Henson, #39,222
Mark H. Weygandt, #43,260
9250 W. 5th Avenue, Suite 200
Lakewood, Colorado 80226
(303) 232-3388

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8

I hereby certify that the foregoing ***PRELIMINARY AMENDMENT*** is being deposited with the United States Postal Service as first class mail, postage prepaid, for delivery in an envelope addressed to the Assistant Commissioner for Patents, Washington, DC 20231 on this 31st day of August, 2001.

Christy L. Byrbank

PROCESS FOR PREPARING POLYAMINES

This invention relates to a process for preparing polyamines and particularly, although not exclusively, relates to a solid phase process and/or a process which can readily be used in a combinatorial or parallel array technique.

Several naturally occurring polyamine amide compounds have shown neurological activity and have glutamate receptor antagonist activity. Hitherto, they have been considered for use in the treatment of neurological disorders such as Alzheimer's disease, Huntingdon's chorea, stroke and brain trauma.

Traditionally, the compounds have been isolated from natural sources such as spider and wasp venom's; however, isolation and purification of the compounds can be problematical.

Attempts have been made to synthesise polyamine amides, for example as discussed in Pharmaceutical Sciences (1997), 3,223-233, Chem Letts (1993) 929-932, Chem Pharm Bull 44(5) 972-979 (1996) and by I.R. March and M. Bradley in Tetrahedron 1997, Vol 53, pages 17317 to 34. In the latter reference, a protected polyamine is prepared in solution and is then attached to a resin and used in a solid phase process. However, the solution preparation is hard, tedious and time-consuming and it is difficult to prepare polyamines in a parallel manner. Consequently, desired amines tend to be made one at a time, using the known art.

It is an object of the present invention to provide an advantageous process for preparation of symmetrical and unsymmetrical polyamines.

According to a first aspect of the invention, there is provided a process for preparing a polyamine compound which includes a step (a) of treating a compound which incorporates a moiety of formula:

SS-NR-R^c-NH- I

with a compound which incorporates a moiety of formula:

-NR^1-R^b-L II

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group -NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

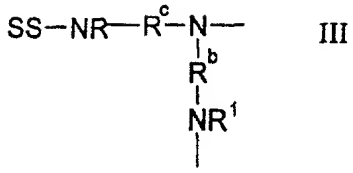
Unless otherwise stated in this specification, where any group is stated to be optionally-substituted, it may be substituted by one or more substituents. Suitably, it may be substituted by up to 4, preferably up to 3, more preferably up to 2, especially up to 1 substituent.

Unless otherwise stated in this specification, where any group is stated to be optionally-substituted, optional substituents may be selected from halogen (preferably fluorine, chlorine or bromine) atoms and optionally substituted, preferably unsubstituted, alkyl, acyl, aryl, nitro, cyano, alkoxy, alkoxyalkyl, hydroxy, amino, alkylamino (including dialkylamino), sulphinyl, alkylsulphinyl, carbamoyl (including alkylcarbamoyl and dialkylcarbamoyl), sulphonyl, alkylsulphonyl, sulphonate, amido, alkylamido, alkoxycarbonyl, halocarbonyl (especially chlorocarbonyl), haloalkoxy, and haloalkyl (especially fluoroalkyl or chloroalkyl), groups.

Unless otherwise stated in this specification, an alkyl, alkenyl, alkylene or alkenylene group may have up to 12, suitably up to 10, preferably up to 8, more preferably up to 6, especially up to 4, carbon atoms.

Unless otherwise stated in this specification, an aryl group is suitably an aromatic or heteroaromatic group which preferably has 6 to 10 ring atoms and, more preferably, has 6 or 10 ring atoms. Examples of aromatic groups include phenyl, 1-naphthyl and 2-naphthyl groups of which the phenyl group is preferred. Heteroaromatic groups may include one or more O, N or S atoms or combinations thereof.

The process suitably produces a compound which incorporates a moiety:



III

which may subsequently be optionally derivatized and/or a compound prepared may be detached from said SS moiety and/or said compound prepared may be optionally derivatized after detachment.

Preferably, R represents a hydrogen atom or an optionally-substituted, preferably an unsubstituted, alkyl group. More preferably, R represent a hydrogen atom.

R^b and R^c may independently have up to 10, suitably up to 8, preferably up to 6, more preferably up to 4, carbon atoms in a straight chain. R^b and R^c may have the same number of carbon atoms in a straight chain in which case compounds which include moiety III (and compounds moieties produced in downstream processes) may be symmetrical polyamines. However, R^b and R^c may have a different number of carbon atoms in a straight chain in which case compounds which include moiety III (and compounds/moieties produced in downstream processes) may be unsymmetrical polyamines. Unsymmetrical polyamines can be quite difficult to prepare by known processes; however, the process described herein can relatively easily be used to make such compounds. Preferably, R^b and R^c independently have 3 or 4 carbon atoms in a straight chain. More preferably, R^c has 4 carbon atoms and R^b has 3 carbon atoms in a straight chain.

R^b and R^c may independently be optionally substituted by 1 or 2 optionally-substituted, preferably unsubstituted, alkyl groups, wherein each alkyl group suitably has 1 to 3 carbon atoms.

R^1 suitably represents a hydrogen atom or a C_{1-10}, preferably C_{1-8}, more preferably C_{1-6}, especially C_{1-4}, alkyl group or an aryl group, said alkyl or aryl group being optionally-substituted, preferably by one or more substituents selected from halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is alkyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof.

Suitably, in said moiety II (and suitably in other moieties which include R^1), R^1 represents a hydrogen atom or an optionally-substituted, preferably an unsubstituted, alkyl or aryl group. Preferably, R^1 represents a hydrogen atom or an optionally-substituted alkyl group.

Said moiety of formula I may be part of a structure of formula:

$$SS\text{-}NR\text{-}R^c\text{-}NHP^1 \qquad IV$$

wherein P^1 represents a protecting/activating group. P^1 is preferably an electron-withdrawing group. It is preferably adapted to increase the acidity of the hydrogen atom of the group $-NHP^1$. P^1 preferably forms a sulphonamide group with moiety I. Thus, P^1 preferably represents a moiety:

$-SO_2-X^1$ V

wherein X^1 represents an optionally-substituted aryl, especially phenyl, group. Said optionally-substituted aryl group may include one or more substituents. Preferred substituents are electron-withdrawing groups. A nitro group is a preferred optional substituent. A 4-nitro or a 2,4-nitro is especially preferred. Preferably, X^1 represents a di-nitrophenyl group.

The mechanism of the reaction of moieties I and II is believed to involve attack of the nucleophilic nitrogen atom of moiety -NH- of moiety I with a carbon atom adjacent to leaving group L in moiety II. L is preferably an electron-withdrawing group. Consequently, the leaving group L is displaced.

L may need to be activated to act as a leaving group in the reaction. L may be any leaving group which may be electronegative and/or be capable of functioning in the mechanism referred to. L may be a halogen atom, preferably a bromine or chlorine atom, especially a bromine atom, or a hydroxy group. The ability of the hydroxy group to act as a leaving group may be caused and/or enhanced by other reagents used in the reaction.

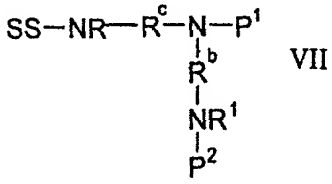
Said moiety of formula II may be part of a structure of formula:

$P^2NR^1-R^b-L$ VI

wherein P^2 represents a protecting group. Preferred protecting groups include N-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl and Triethlsilyloxycarbonyl (TEOC). The former is preferred.

Preferably, SS represents a solid support resin which includes linking means. Said linking means may include a -O-CO- moiety, the carboxy end of which is suitably bonded to the nitrogen atom of the moiety -NR- of moiety I. The alkoxy end of the -O-CO- moiety may be bonded to the resin by suitable means which is preferably an alkylene group, especially a $-CH_2-$ group. Said solid support resin may be any suitable resin, for example a polystyrene resin. Suitably, the linking means is a Wang linker.

In Step (a), swollen resin of formula I (which may suitably be swollen in anhydrous tetrahydrofuran), triphenylphosphine and a said compound which incorporates moiety II (especially compound VI) may be stirred together and, subsequently, a coupling agent, suitably diethylazodicarboxylate, is added, slowly. The mixture may be stirred for about 12 hours, filtered, washed and dried. The product of the reaction suitably incorporates moiety III and is suitably protected by groups P^2 and P^1 and is, therefore, of formula:



VII

Said compound VI may be prepared by a reaction known to a person skilled in the art, wherein P^2 is a protecting group.

Said compound IV may be prepared in a step (-b) which comprises reaction of a compound of general formula:

$$SS\text{-}NR\text{-}R^c\text{-}NH_2 \qquad VIII$$

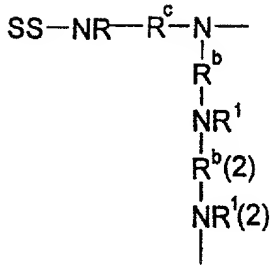
with a compound of formula P^1L^2 wherein L^2 is a leaving group, especially a chlorine atom. The reaction is preferably carried out in the presence of a base, for example 2,6-lutidine and in an organic solvent.

Said compound of formula VIII may be prepared in a step (-c) by reaction of a compound of formula

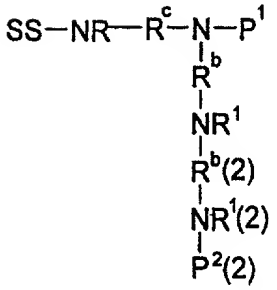
$$HRN\text{-}R^c\text{-}NH_2 \qquad IX$$

with a structure $SS\text{-}L^3$ wherein L^3 represents a leaving group which may include an imidazole moiety.

Compound VII and/or said compound incorporating moiety II can readily be derivatised to produce a wide range of compounds, suitably in a parallel array or combinatorial chemistry technique. In a first embodiment, compound VII and/or said compound incorporating moiety III may be treated with a further compound which incorporates a moiety of formula II (which moiety may include R^1, R^b and L which are the same as or different to such groups used in Step (a)) as described above thereby to prepare a compound which incorporates the moiety



or is of formula



wherein $R^b(2)$, $R^1(2)$ and $P^2(2)$ may be any group described herein for R^b, R^1 and P^2 respectively except that they may be the same or different to groups R^b and R^1 used in Step (a) and P^2 as described above.

In the derivatisation reaction of the first embodiment, said compound of formula VII may be reacted to remove P^1 and replace it with, for example another protecting group (e.g. Boc) and P^2 may be removed and replaced with a protecting/activating group of type P^1 discussed above. The derivatised compound VII prepared

may then be treated, for example with a structure of formula:

$P^2NR^1(2)-R^b(2)-L$

wherein P^2 and L are as described above (although they could be different from P^2 and L used in Step (a)). The reaction may be carried out under conditions as described above for Step (a).

The derivatisation of the first embodiment may be further repeated to add successive groups $-NR^1(3)-R^b(3)-$ etc.

Compound VII (or derivatives thereof prepared as described in said first embodiment) may be derivatized by a range of compounds, for example amino acids, may be coupled to moiety $-NR^1-$ (or $-NR^1$ (2), $-NR^1$ (3) if provided), thereby replacing protecting group P^2 and, in turn, other compounds, for example further amino acids, may be coupled to said compounds initially coupled to moiety $-NR^1-$ (or $-NR^1$ (2), $-NR^1$ (3), if provided) and/or derivatisation reactions effected. Further coupling reactions may also be effected by techniques known to those skilled in the art.

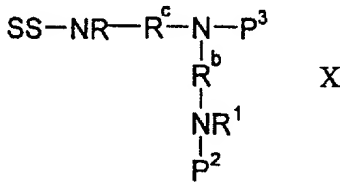
In general terms, a suitably deprotected compound VII and/or said compound incorporating moiety III may be treated with a first reagent (which may be protected) to replace group P^2 in compound VII with a residue of said first reagent. The product (or a derivative), suitably deprotected, may be treated with a second reagent (which may be protected) so that said second reagent becomes

bonded to a said residue of said second reagent. Such treatments may be repeated to react further reagents with the derivative of compound VII.

Suitably, said first reagent is di-functional. Said first reagent preferably includes an aryl group (or a precursor thereof). Said first reagent preferably includes an amine group (or a precursor thereof). Thus, suitably said first reagent (and a or any subsequent reagent) is an amino acid (or a precursor thereof, for example a protected version or derivative thereof).

Suitably, said second reagent is di-functional. Said second reagent preferably includes an aryl group (or a precursor thereof). Said second reagent preferably includes an amine group (or a precursor thereof). Thus, suitably said second reagent is an amino acid (or a precursor thereof, for example a protected version or derivative thereof). Further reagents which may be reacted with said second reagent may have any feature of said second reagent as described above.

More specifically, said compound of formula VII may be reacted in a step (b) to substitute the group P^1 with another group which may be another protecting group P^3 or an electrophilic reagent. Group P^3 may be an acyl, -Boc, alkyl, or sulphonyl group. Thus, the product of step (b) may be a compound of formula



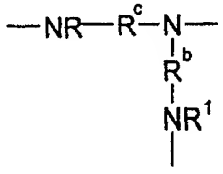
X

Protecting group P^2 may next be removed from compound (X) in a step (c) so that P^2 is replaced by a hydrogen atom (such a compound being referred to as compound XI). Step (c) may involve reaction in hydrazine and an organic solvent or may involve any suitable deprotection reaction.

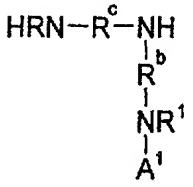
Next, in Step (d), a compound may be coupled to the free $-NH_2$ group of compound XI. For example, an amino acid, suitably an amino acid which is protected by a protecting group orthogonal to the group binding portions of compound X to the solid support of SS, such as an Fmoc protected amino acid (i.e. "Fmoc AA"), may be coupled to said free $-NH_2$ group. Suitably, an amino acid selected from those shown in Summary 1 or Summary 2 hereinafter, especially those in Summary 1, may be coupled to said group. Thereafter, other compounds, for example other amino acids, may be coupled, for example to the aforementioned amino acid, in order to produce more complex compounds using procedures know to those skilled in the art. Suitably, an amino acid selected from those shown in Summary 1 or Summary 2 hereinafter, especially those in Summary 2, may be coupled.

Subsequently, the desired compound prepared may be cleaved from the resin and/or optionally derivatised as may be desired.

Such a compound may incorporate a moiety

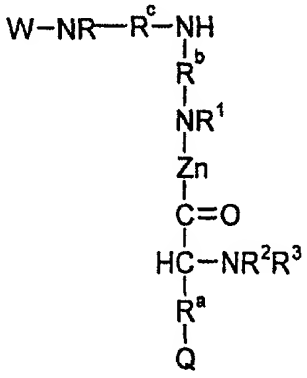


Preferably such a compound is of general formula



wherein A^1 is a substituent group which may comprise one or more optionally derivatised amino acid residues or is a salt of the aforementioned compound.

More preferably, such a compound may be of formula



wherein R, R^c, R^b and R^1 are as described in any statement herein; W is a hydrogen atom or an optionally-substituted, preferably unsubstituted, alkyl or aryl group; Z is an amino acid residue, especially an aromatic amino acid residue; n is zero or a positive integer, preferably in the range 0-10, more preferably 0-4, especially 0 to 1; R^2 and R^3 are the same or different from each other and each represents a hydrogen atom or a

group of formula R^6, R^6CO-, R^6OCO- or R^6NHCO- where R^6 represents an optionally-substituted alkyl group, suitably a C_{1-10}, preferably a C_{1-8}, more preferably a C_{1-6}, especially a C_{1-4}, alkyl group, or an optionally-substituted aryl group, wherein preferred optional substituents of said alkyl and aryl groups are selected from halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is alkyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof; R^a represents an optionally-substituted straight or branched chain alkylene or alkenylene group, preferably an alkylene or alkenylene group having 1 to 6 carbon atoms each optionally-substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms; and Q represents an amidino group, a cyano group or a group of formula XYN-, wherein X and Y are the same or different, and each may represent a hydrogen atom, an alkyl group, (suitably a C_{1-10}, preferably a C_{1-8}, more preferably a C_{1-6}, especially a C_{1-4} alkyl group) or a simple heteroatom-containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group.

The process described according to said first aspect may be used to prepare any of the polyamine compounds described in any of the documents cited in the introduction of this specification; and any of the polyamine compounds described in PCT/GB89/03775 and the polyamine compounds described in each of the aforementioned documents are incorporated herein by reference.

According to a second aspect of the invention, there is provided a process for preparing a plurality of different polyamine compounds which includes a step of:

(a) selecting a plurality of different compounds of general formula I or a plurality of different compounds of formula II or a plurality of different compounds of both formulas I and II and reacting compounds of formula I with compounds of formula II, for example in a combinatorial or parallel array technique, followed by optional derivatisation, thereby to prepare a plurality of different polyamine compounds; OR

(b) derivatising a product of a reaction of a compound of general formula I with a compound of general formula II with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds.

According to a third aspect of the invention, there is provided a library of compounds prepared in a process according to said second aspect.

According to a fourth aspect of the invention, there is provided a product of a process according to said first or second aspect.

According to a fifth aspect of the invention, there is provided any novel intermediate described in any statement herein.

Any feature of any aspect of any invention or embodiment described herein may be combined with any

feature of any aspect of another invention described herein.

Specific embodiments of the invention will now be described, by way of example. In the Examples, the following abbreviations are used:

Arg	arginine;
Boc	t-butoxycarbonyl;
DCM	dichloromethane
Dde	N-1,4(4,4-dimethyl-2,6-dioxocyclohex-1-ylidine) ethyl;
DEAD	diethyl azodicarboxylate;
DIC	di-isopropylcarbodiimide;
DMF	dimethylformamide;
Fmoc	N-fluorenylmethoxycarbonyl;
HOBt	N1-hydroxybenzotriazole;
Lys	lysine;
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl;
Phe	phenylalanine;
RP-HPLC	reverse phase high performance liquid chromatography;
THF	tetrahydrofuran;
TFA	trifluoracetic acid;
TBTU	2(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEOC	2-(Trimethylsilyl)ethoxycarbonyl.

Example 1 - Preparation of Arginine-L-phenylalanine-spermidine - an unsymmetrical polyamine.

Wang resin (0.03 mmol, 50 mg) was swollen in anhydrous tetrahydrofuran (1.0 ml) and carbonyl diimidazole (4 equivalents, 0.12 mmol, 19 mg) was added. The resulting mixture was then stirred at ambient temperature for 16 hours, after which it was filtered and washed with tetrahydrofuran, ethanol and dichloromethane. The resin was then dried in *vacuo*.

The resin was re-swollen in anhydrous dichloromethane (1.0 ml), and 1,4-diaminobutane (10 equivalents, 0.3 mmol, 25 mg) were added. The resulting mixture was stirred for 2 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane), after which it was dried in *vacuo*.

The resin was again swollen in anhydrous dichloromethane (1.0 ml), and 2,6-lutidine (5 equivalents, 0.15 mmol, 16 mg) were added, followed by the careful addition of 2,4-dinitrobenzenesulfonyl chloride (4 equivalents, 0.12 mmol, 32 mg). The mixture was stirred under an inert atmosphere for 2 hours and then washed (dimethylformamide, methanol, dichloromethane) and dried in *vacuo*.

The resulting resin was then swollen in anhydrous tetrahydrofuran (1.0 ml) and triphenylphosphine (4 equivalents, 0.12 mmol, 32 mg). Dde-protected aminoalcohol (4 equivalents, 0.12 mmol, 29 mg) (prepared as described below) were added and dissolved with stirring. Diethyl azodicarboxylate (4 equivalents, 0.12

mmol, 21 mg) was added dropwise and the mixture was stirred for 12 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane). It was then dried in *vacuo*.

The resin was then swollen in dichloromethane (1.0 ml), and propylamine (5 equivalents, 0.15 mmol, 13 mg) was added. The mixture was then stirred for 1 hour after which it was filtered and washed (dimethylformamide, methanol, dichloromethane) and then dried in *vacuo*.

The resin was again swollen in dichloromethane (1.0 ml), and di-t-butyl dicarbonate (10 equivalents, 0.3 mmol, 33 mg) and N,N-dimethylaminopyridine (5 mol%, 0.0015 mmol, 0.2 mg) were added, and the mixture was stirred for 16 hours. The resin was then filtered and washed (dimethylformamide, methanol, dichloromethane), and then dried in *vacuo*.

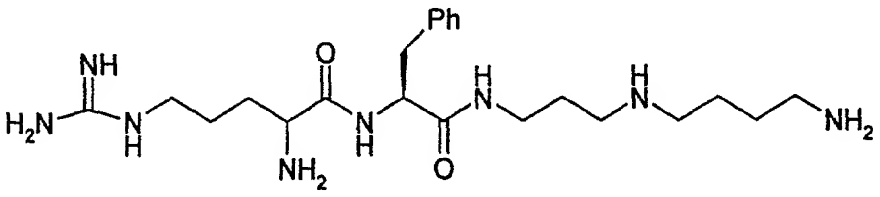
The resin was then stirred in 2% hydrazine hydrate/dimethylformamide (1.0 ml) for 1 hour and then washed (dimethylformamide, methanol, dichloromethane), after which it was dried in *vacuo*.

Fmoc-Phe-OH (4 equivalents, 0.12 mmol, 46 mg), TBTU (4 equivalents, 0.12 mmol, 39 mg) and diisopropylethylamine (8%, 0.48 mmol, 62mg) were dissolved in anhydrous dimethylformamide (1.0 ml), and the mixture was added to the resin. The whole was then stirred for 12 hours, and then filtered and washed (dimethylformamide, methanol, dichloromethane) and dried in *vacuo*.

To the resin was added 20% piperidine/dimethylformamide (1.0 ml) and the mixture was stirred for 0.5 hour. It was then filtered and washed (dimethylformamide, methanol, dichloromethane) and then dried in *vacuo*.

Boc-Arg(Pbf)-OH (4 equivalents, 0.12 mmol, 63 mg), TBTU (4 equivalents, 0.12 mmol, 39 mg), and diisopropylethylamine (8 equivalents, 0.48 mmol, 62 mg) were dissolved in dimethylformamide (1.0 ml) and the mixture was added to the resin. The whole was then stirred for 12 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane). It was then dried in *vacuo*.

50%TFA/45%dichloromethane/2.5%H_2O/2.5% triisopropylsilane (1.0 ml) was added to the resin and the mixture was stirred for 1 hour. The resin was filtered and washed with dichloromethane (1.0 ml) and the filtrate was concentrated in *vacuo*. The resulting viscous yellow oil was triturated with anhydrous diethyl ether (3x2 ml) to yield the title compound as shown below as its tetrakis TFA salt (19 mg, 70%):

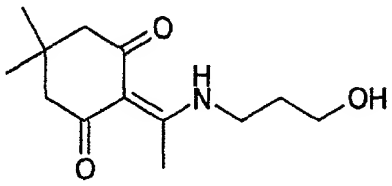


Analysis:

LCMS - 90% (ELS detection). M/z 449 (ES^+).

NMR:- ^1H NMR was found to be in accordance with the above structure

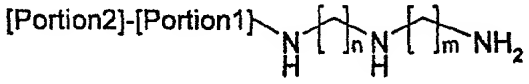
In the above described process, the following Dde protected aminoalcohol was used:



The Dde protected aminoalcohol was prepared as follows: To a solution of 3-amino-1-propanol (1.5 g, 20 mmol) in ethanol was added 2-acetyl dimedone (1.1 equivalents, 22 mmol, 4.0 g) and the mixture was heated to 50°C for 1 hour. The resulting solution was concentrated in *vacuo* to yield a red crystalline solid that was triturated with hexane to afford an off-white solid (4.74g, 95%).

Examples 2 - Preparation of other polyamines

Polyamines having the general structure:



E-I

wherein Portions 1 and 2 are amino acid residues as described hereinafter and wherein n represents 3 or 4 and m represents 4 were prepared using the following general method which is summarised in Scheme 1.

Step 1

Wang resin (0.03 mmol) was swollen in anhydrous THF (1.0 ml) and carbonyl diimidazole (4 eq, 0.12 mmol) added portionwise. The resulting mixture was stirred at ambient temperature for 16 hours then filtered and washed with THF, Et_2O and DCM. The resin was then dried in *vacuo* (Step 1).

Step 2

The resin was re-swollen in anhydrous DCM (1.0 ml) and a symmetrical diamine (NH_2-$(CH_2)_m$-NH_2) (10 eq, 0.3 mmol) added portionwise. The resulting mixture was stirred for 2 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 3

The resin was again re-swollen in anhydrous DCM (1.0 ml) and 2,6-lutidine (5 eq, 0.15 mmol) added followed by the careful addition of 2,4-dinitrobenzenesulfonyl chloride (4 eq, 0.12 mmol). The mixture was stirred under an inert atmosphere for 2 hours then washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 4

The resulting resin was then swollen in anhydrous THF (1.0 mol) and triphenylphosphine (4 eq, 0.12 mmol), Dde-protected aminoalcohol (DdeHN-$(CH_2)_n$-OH) (4 eq, 0.12 mmol) were added and dissolved with stirring.

Diethylazodicarboxylate (4 eq, 0.12 mmol) was added dropwise and the mixture stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 5

The resin was then swollen in DCM (1.0 ml) and n-propylamine (5 eq, 0.15 mmol) added and the mixture stirred for 1 hour then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

The resin was again swollen in DCM (1.0 ml) and di-t-butyldicarbonate (10 eq, 0.3 mmol) and N,N-dimethylaminopyridine (5 mol%, 0.0015 mmol) added and the mixture stirred for 16 hours. The resin was then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 6

The resin was then stirred in 2% hydrazine hydrate/DMF (1.0 ml) for 1 hour then washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 7

The Fmoc derivatives of the amino acids shown in Summary 1 (wherein residues thereof are destined to become Portion 1 in the polyamines) were prepared (hereinafter referred to, generally, as "Fmoc AA1"). Then, Fmoc AA1 (4 eq, 0.12 mmol), TBTU (4 eq, 0.12 mmol) and diisopropylethylamine (8 eq, 0.48 mmol) were dissolved in anhydrous DMF (1.0 ml) and the mixture added to the resin.

The whole was then stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 8

To the resin was added 20% piperidine/DMF (1.0 ml) and the mixture stirred for 0.5 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

The Boc derivatives of the amino acids shown in Summary 2 (wherein residues thereof are destined to become Portion 2 in the polyamines) were prepared (hereinafter referred to, generally, as "Boc AA"). Then, Boc AA (4 eq, 0.12 mmol), TBTU (4 eq, 0.12 mmol), and diisopropylethylamine (8 eq, 0.48 mmol) were dissolved in DMF (1.0 ml) and the mixture added to the resin. The whole was then stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 9

50%TFA/45%DCM/2.5%H_2O/2.5% triisopropylsilane (1.0 ml) was added to the resin and the mixture stirred for 1 hour to remove the compound from the resin (Step 9). The resin was filtered and washed with DCM (1.0 ml) and the filtrate concentrated in *vacuo*. The resulting viscous yellow oil was triturated with anhydrous diethylether (3x2 ml) to yield the required compound.

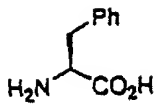
A wide range of compounds were prepared using the general method described and using the amino acids in Summary 1 to provide Portion 1 and the amino acids in Summary 2 to provide Portion 2. It will be appreciated

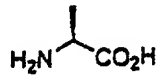
that amino acid residues incorporated into compound E-I comprise the amino acids shown in Summary I and II but excluding hydrogen atoms from the $-NH_2$ and $-CO_2H$ groups.

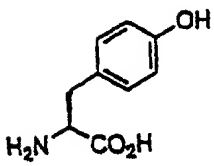
Table 1 summarises a 4,4-polyamine library prepared - that is, a library wherein n and m represent 4; the left column in the table details respective Portion 1's (identified by their letters in Summary 1) used to prepare the compounds; and the top row details respective Portion 2's (identified by their numbers in Summary 2) used to prepare the compounds. Table 2 summarises a 3,4-polyamine library - that is, wherein n represents 3 and m represents 4 with Portions 1 and 2 being identified as before.

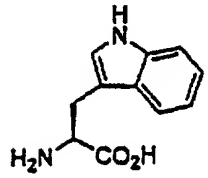
In tables 1 and 2, each box in the table represents a particular compound prepared and the Mass Spec (ES^+) and HPLC Retention Time in minutes are provided in each box (where available).

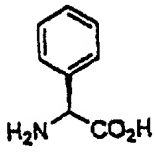
Summary 1 - amino acids used to form "Portion 1" amino acid residues.

A 

B 

C 

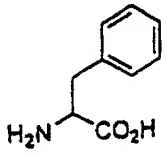
D 

E 

F Portion 1 absent

Summary 2 - amino acids used to form "Portion 2" amino acid residues.

1



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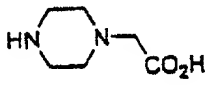

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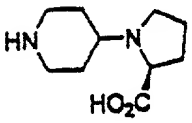

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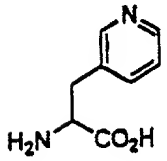

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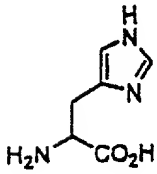

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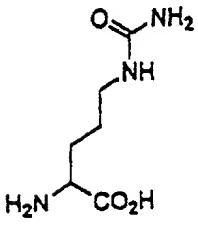

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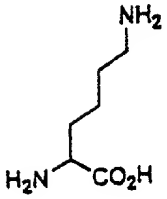

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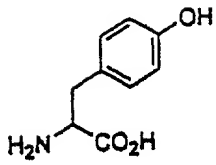

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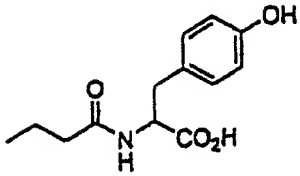

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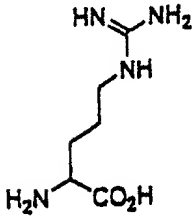

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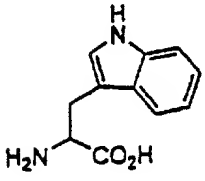

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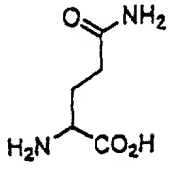
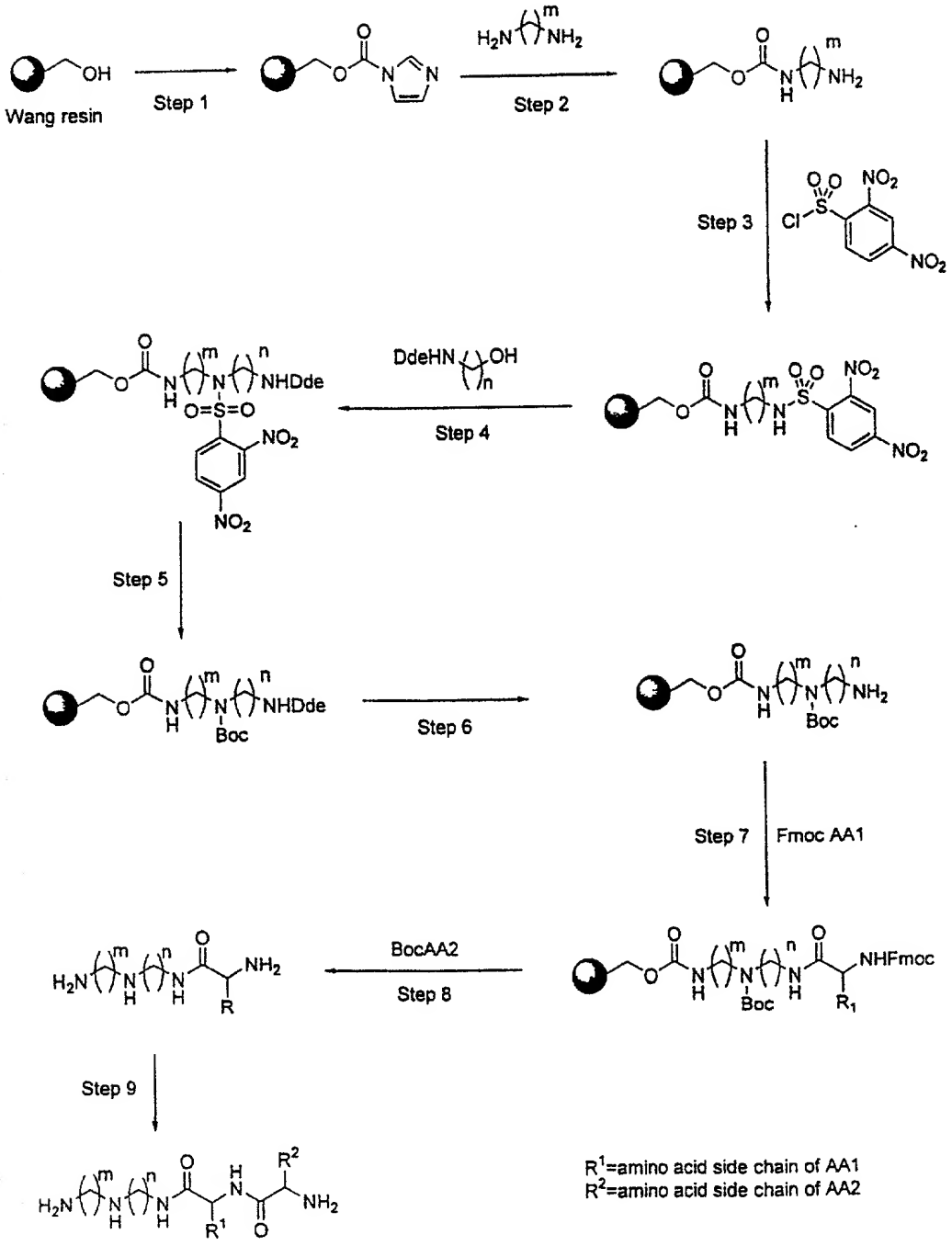


	1	2	3	4	5	6	7	8	9	10	11	12
A	454.17 0.27	433 0.23	487.29 0.24	455 0.24	444 0.26	464 0.26	435 0.25	470 0.26	540 0.49	463 0.25	493 0.29	-
B	378 0.25	357 0.25	411 0.22	379 0.25	368 0.22	388 0.25	359 0.25	394 0.25	464 0.37	387 0.22	417 0.25	-
C	470 0.25	449 0.25	503 0.25	471 0.25	460 0.25	480 0.25	451 0.25	486 0.25	556 0.44	479 0.22	509 0.26	-
D	493 0.26	472 0.25	526 0.23	494 0.25	483 0.22	-	474 0.25	509 0.26	-	502 0.22	-	-
E	-	419 0.24	473 0.25	441 0.25	430 0.24	450 0.24	421 0.26	456 0.26	526 0.48	449 0.23	-	-
F	307 0.25	286 0.25	340 0.25	308 0.25	297 0.23	317 0.25	288 0.22	323 0.23	393 0.35	316 0.23	346 0.25	-

TABLE 1 - 4,4-Polyamine Library.

	1	2	3	4	5	6	7	8	9	10	11	12
A	440.2 0.29	419.2 0.27	473.28 0.26	441.17 0.27	430.2 0.24	450.22 0.27	421.26 0.27	456.21 0.29	526.26 0.5	449.21 0.25	-	-
B	-	343.25 0.26	397.29 0.26	365.24 0.26	354.25 0.26	374.25 0.25	345.25 0.26	380.22 0.26	450.23 0.38	373.3 0.26	403.23 0.26	345.28 0.27
C	456.2 0.27	435.22 0.27	487.28 0.25	457.19 0.21	446.19 0.26	466.24 0.25	437.22 0.27	472.24 0.26	542.24 0.45	465.25 0.27	495.24 0.26	-
D	479.16 0.25	458.18 0.26	412.29 0.26	480.22 0.26	469.26 0.24	489.24 0.26	460.27 0.24	-	565.21 0.5	488.3 0.26	518.2 0.31	460.24 0.26
E	426.21 0.26	405.22 0.26	459.25 0.27	427.18 0.27	416.17 0.26	436.2 0.26	407.24 0.26	442.2 0.28	512.25 0.5	435.22 0.26	-	407.21 0.26
F	293.18 0.26	272.22 0.25	326.25 0.27	294.17 0.26	283.17 0.27	303.2 0.26	274.23 0.25	309.13 0.25	379.22 0.35	302.19 0.26	332.14 0.26	274.19 0.24

TABLE 2 – 3,4-Polyamine Library.


Wang resin
Step 1
Step 2
Step 3
Step 4
Step 5
Step 6
Step 7
Fmoc AA1
Step 8
BocAA2
Step 9
DdeHN
OH
NHDde
NHFmoc
Boc
R^1=amino acid side chain of AA1
R^2=amino acid side chain of AA2

Example 3 - Alternative reagent for Step 4

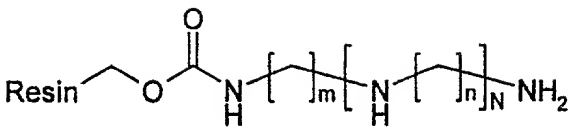
As an alternative to the use of Dde-protected aminoalcohols in Step 4, TEOC may be used.

Example 4 - Derivatives of polyamines

Derivatives of the amines prepared in Examples 1 and 2 may be prepared by reaction with a compound having an electrophilic specie such as an acid chloride, sulphonyl chloride etc. In a specific example, the starting material of Step 5 may be acylated, instead of using di-t-butyldicarbonate to give a Boc protecting group. Acylation may be carried out using a standard technique, using an acid chloride or another activated acid, to produce peptidomimetics. Sulphonyl chlorides may be used to sulphonylate amine groups to produce derivatives.

Example 5

Step 4 in Example 4 may be repeated more than once in order to add further moieties $-NH-(CH_2)_n-$ to the polyamine chain. To this end, after Step 5 in Scheme 1, the Dde group may be removed and the resultant free amine group re-sulphonated in a process analogous to that described in Step 3. The re-sulphonated product may then be treated with a Dde-protected amine alcohol in a process analogous to that described in Step 4. Step 5 may be repeated. Subsequently, further moieties $-NH-(CH_2)_n-$ may be added in the manner described or Step 6 and subsequent steps described may be carried out. Thus, the product of Step 6 may be of formula



wherein N is an integer of 1 or greater and wherein n may be the same or different for each repeat unit N.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features

disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

5

CLAIMS

1. A process for preparing a polyamine compound which includes a step (a) of treating a compound which incorporates a moiety of formula:

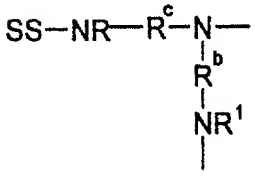
$$SS\text{-}NR\text{-}R^c\text{-}NH\text{-} \qquad I$$

with a compound which incorporates a moiety of formula:

$$-NR^1\text{-}R^b\text{-}L \qquad II$$

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group -NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

2. A process according to claim 1, wherein said process produces a compound which incorporates a moiety:



III

3. A process according to claim 1 or claim 2, wherein said moiety of formula I is part of a structure of formula:

$$SS\text{-}NR\text{-}R^{c}\text{-}NHP^{1} \qquad IV$$

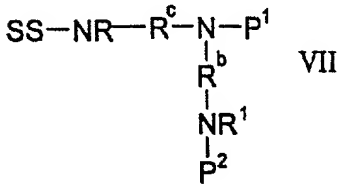
wherein P^1 represents a protecting and/or activating group.

4. A process according to any preceding claim, wherein said moiety of formula II is part of a structure of formula:

$$P^2NR^1\text{-}R^b\text{-}L$$

wherein P^2 represents a protecting group.

5. A process according to any preceding claim, wherein the product of the reaction of moieties of formula I and II is of formula



VII

wherein P^1 represents a protecting and/or activating group and P^2 represents a protecting group.

6. A process according to any preceding claim, wherein the polyamine prepared by reacting moieties I and II and/or moiety III and/or moiety VII are derivatised in a subsequent process step.

7. A process according to claim 6, wherein derivatisation involves treatment with a first reagent in order to incorporate a residue of said first reagent into said polyamine.

8. A process according to claim 7, wherein said first reagent is difunctional.

9. A process according to claim 7 or claim 8, wherein said first reagent includes an amine group or a precursor of an amine group.

10. A process according to any of claims 7 to 9, wherein said first reagent is an amino acid or a precursor thereof.

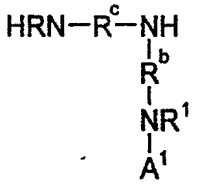
11. A process according to any of claims 7 to 10, wherein said polyamine is derivatised with a second reagent.

12. A process according to any preceding claim, wherein R represents a hydrogen atom or an optionally-substituted alkyl group; R^b and R^c independently have up to 10 carbon atoms in a straight chain; R^1 represents a hydrogen atom or an optionally-substituted C_{1-10} alkyl group or an optionally-substituted aryl group.

13. A process according to any preceding claim, wherein L is an electron-withdrawing group.

14. A process according to any preceding claim, wherein L represents a halogen atom or an hydroxy group.

15. A process according to any preceding claim, wherein the compound prepared in the process is of general formula



wherein A^1 is a substituent group.

16. A process for preparing a plurality of different polyamine compounds which includes a step of:

(a) selecting a plurality of different compounds which include moiety I and/or a plurality of different compounds which include moiety II and reacting compound(s) of formula I with compound(s) of formula II, followed by optional derivatisation thereby to prepare a plurality of different polyamine compounds; OR

(b) derivatising a product of a reaction of a moiety I with a moiety II with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds;

wherein moieties I and II are as described in any preceding claim.

17. A library of compounds prepared in a process according to claim 16.

18. A product of a process described in any of claims 1 to 16.

19. Any novel intermediate of a process described in any of claims 1 to 16.

PTO/SB/01 (03-01)
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	1768
First Named Inventor	Lloyd J. Payne
COMPLETE IF KNOWN	
Application Number	09 / 868,441
Filing Date	June 18, 2001
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROCESS FOR PREPARING POLYAMINES

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 06/18/2001 as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
PCT/GB98/03775		12/16/1998	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

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DECLARATION — Utility or Design Patent Application

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NAME OF SOLE OR FIRST INVENTOR : [ ] A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Lloyd J. | Family Name or Surname Payne

Inventor's Signature | Date 28 Sept 2001

Residence: City | State | Country GB | Citizenship GB

Mailing Address 73 Frank Bridges Close, Soham, Ely, Cambridgeshire CB7 5EZ GBX

City | State | ZIP | Country GB

NAME OF SECOND INVENTOR: [ ] A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Neal D. | Family Name or Surname Hone

Inventor's Signature N. Hone | Date 28 Sept 01

Residence: City | State | Country GB | Citizenship GB

Mailing Address 2 Beech Close, Southam, Leamington SPA CV33 OHU GBX

City | State | ZIP | Country GB

[ ] Additional inventors are being named on the ___supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

Please type a plus sign (+) inside this box → [+]

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Application Number	09/868,441
Filing Date	June 18, 2001
First Named Inventor	
Title	PROCESS FOR PREPARING POLYAMINES
Group Art Unit	
Examiner Name	
Attorney Docket Number	1768

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[ ] Firm or Individual Name	Timothy J. Martin, P.C.				
Address	9250 W. 5th Avenue, Suite 200				
Address					
City	Lakewood,	State	Colorado	Zip	80226
Country	USA				
Telephone	(303) 232-3388	Fax	(303) 232-3288		

I am the:

[X] Applicant/Inventor.

[ ] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	Lloyd J. Payne
Signature	
Date	28th September 2001

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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Address	9250 W. 5th Avenue, Suite 200				
Address					
City	Lakewood,	State	Colorado	Zip	80226
Country	USA				
Telephone	(303) 232-3388	Fax	(303) 232-3288		

I am the:

[X] Applicant/Inventor.

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SIGNATURE of Applicant or Assignee of Record

Name	Neal D. Hone
Signature	N. Hone
Date	28 Sep 01

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